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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,236	11/04/2003	Brenda F. Baker	ISIS-5207	5280

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EXAMINER

VIVLEMORE, TRACY ANN

ART UNIT	PAPER NUMBER
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1635

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/701,236

Applicant(s)

BAKER ET AL.

Examiner

Tracy Vivlemore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,7-9,11,13-24,26,27,36,38-52,59,62 and 68 is/are pending in the application.
- 4a) Of the above claim(s) 11,13-24,26,27,36 and 38-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,7-9,59,62 and 68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 11/6/06

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions and status of the application

Claims 11, 13-24, 26, 27, 36 and 38-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 17, 2006.

Claims 2-6, 10, 12, 25, 28-35, 37, 53-58, 60, 61 and 63-67 have been canceled in the amendment filed 12/19/06. Claims 1, 7-9, 59, 62 and 68 are examined on the merits.

Response to arguments: Priority

The priority date accorded this application remains November 5, 2002, the filing date of application 60/423,760. Applicants argue the instantly claimed invention is fully supported by the specification of application 08/870,608, filed June 6, 1997. To support this argument applicants point to portions of the '608 specification as evidence of contemplation of sense and antisense oligomers of 12-30 nucleotides that are not covalently linked and these portions do appear to provide support for those specific limitations. Applicants further point to page 6 of the '608 application as generically

disclosing modifications to ribonucleosides that improve pharmacokinetic properties. Applicants assert that those skilled in the art would recognize that 4'-thioribonucleosides have this property, citing two publications. This is not persuasive because applicants do not point to any portion of the '608 application that discloses 4'-thioribonucleosides or which indicates oligomers comprising 4'-thioribonucleosides were specifically contemplated as part of the invention.

Double Patenting

The provisional obviousness-type double patenting rejection over claim 24 of copending Application No. 10/700,697 is withdrawn in view of the cancellation of this claim.

Claim Rejections - 35 USC § 103

Claims 1, 7-9, 59, 62 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 2004/0029275, of record) in view of Barascut et al. (US 5,639,873, of record).

The claimed invention is directed to compositions comprising sense and antisense oligomers that are not covalently linked wherein each strand comprises at least one 4'-thioribonucleoside. In specific embodiments the second oligomer comprises a plurality of ribose nucleosides, the oligomers are formulated as a composition with a pharmaceutically acceptable carrier and the oligomers are 100% complementary over at least 17 contiguous nucleotides. The claimed invention is also

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directed to methods of modulating expression of a target nucleic acid by administering these oligomeric compounds to a cell *in vitro*.

Brown et al. teach siRNAs and methods of using these siRNAs to inhibit gene expression. At paragraphs 21-23, Brown et al. teach the siRNAs can be 15-1000 nucleotides in length, explicitly teaches they are at least 17 nucleotides and teaches they can be fully complementary. At paragraph 152 they teach the siRNAs of the invention comprise modified nucleotides that include derivatives or analogs of 5 carbon sugars. Brown et al. do not explicitly teach their siRNAs comprise 4'-thionucleosides.

It was well known in the art at the time of invention that sugar-modified nucleosides are useful for stabilization of therapeutic nucleic acids. Barascut et al. teach one such sugar-modified nucleoside in the form of 4'-thionucleosides, a sugar-modified nucleoside where the furanose oxygen is substituted with sulfur. At column 2, lines 47-64 Barascut et al. teach that oligonucleotides comprising 4'-thionucleosides in either the ribonucleotide or deoxyribonucleotide forms have increased solubility and stability as compared with oligonucleotides without the modified sugar. Barascut et al. also suggest such oligonucleotides would have increased cellular uptake due to the increased lipophilic character of the sulfur substitution.

It would have been obvious to one of ordinary skill in the art at the time of invention to make the siRNAs comprising modified nucleotides taught by Brown et al. with the 4'-thionucleosides taught by Barascut et al. It would have been further obvious to use these oligonucleotides to decrease expression of a target nucleic acid in a cell. Brown et al. provide a motivation to make siRNAs with nucleotide modifications by

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explicitly suggesting such modifications and provide a motivation to use these oligonucleotides to inhibit gene expression by both suggesting and exemplifying such use. Barascut et al. provide a motivation to make an oligonucleotide comprising 4'-thionucleosides by teaching that such substitution provides an oligonucleotide with increased solubility and increased stability due to increased affinity for a target nucleic acid. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Brown et al. and Barascut et al. because methods of producing modified oligonucleotides are well-known and routinely used in the art and because methods of inhibiting gene expression using such oligonucleotides are also well-known in the art.

Thus, the invention of claims 1, 7-9, 59, 62 and 68 would have been obvious, as a whole, at the time of invention.

Response to arguments

Applicants assert Brown et al. is not a proper prior art reference because the instant application has a priority date of June 6, 1997. This argument is not persuasive because the priority date for the application is November 5, 2002 for the reasons described above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
March 7, 2007

A handwritten signature in black ink, appearing to read 'R. Schnizer', with a stylized, looping flourish at the end.

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER